Temporal Lobe Morphology in Childhood-Onset Schizophrenia

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Objective: *Neurodevelopmental models of schizophrenia imply that a more severe early brain lesion may produce earlier onset of psychotic symptoms. The medial temporal lobes have been proposed as possible locations for such a lesion. The authors tested this hypothesis in a group of children and adolescents with childhood-onset schizophrenia who had severe, chronic symptoms and who were refractory to treatment with typical neuroleptics.* *Method:* *Anatomic brain magnetic resonance imaging scans were acquired with a 1.5-T scanner for 21 patients (mean age=14.6 years, SD=2.1) who had onset of schizophrenia by age 12 (mean age at onset=10.2, SD=1.5) and 41 normal children. Volumes of the temporal lobe, superior temporal gyrus, amygdala, and hippocampus were measured by manually outlining these structures on contiguous 2-mm thick coronal slices.* *Results:* *Patients with childhood-onset schizophrenia had significantly smaller cerebral volumes. With no adjustment for brain volume, no diagnostic differences were observed for any temporal lobe structure. Unexpectedly, with adjustment for total cerebral volume, larger volumes of the superior temporal gyrus and its posterior segment and a trend toward larger temporal lobe volume emerged for the patients with schizophrenia. These patients lacked the normal (right-greater-than-left) hippocampal asymmetry.* *Conclusions:* *These findings do not indicate a more severe medial temporal lobe lesion as the basis of very early onset of schizophrenia.*

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Neurodevelopmental hypotheses of schizophrenia posit that schizophrenia is the result of the interaction of disrupted fetal brain development with normal or abnormal brain maturational changes during late adolescence (1–3). Support for these hypotheses has come from clinical, postmortem, and in vivo brain imaging studies of patients with late-adolescent-onset or early-adult-onset schizophrenia (1). The study of patients with childhood-onset schizophrenia, however, may offer unique opportunities to test neurodevelopmental hypotheses.

Studies of children and adolescents with early-onset schizophrenia (4–7) have demonstrated clinical continuity with the later-onset disorder, with more severe premorbid impairment (4, 8) and a more chronic course (5). These findings might reflect a more severe genetic and/or environmental neurodevelopmental insult, leading to earlier onset.

Evidence from a rat model of schizophrenia involving neonatal ventral hippocampal lesions (9), for example, is consistent with such a formulation. Using this model, Lipska and Weinberger (10) have demonstrated that the timing of emergence of behavioral effects of these lesions is influenced by genotype (strain) and lesion size, with larger lesions causing earlier onset as well as more severe behavioral effects in one of two strains examined.

Our earlier systematic quantitative brain magnetic resonance imaging (MRI) study of patients with childhood-onset schizophrenia (11) revealed significantly smaller total cerebral volume and midsagittal thalamic area; larger caudate, putamen, and globus pallidus volumes; a trend toward larger lateral ventricular volumes; and no diagnostic differences in frontal volume. These findings support clinical studies indicating continuity between childhood-onset and later-onset schizophrenia (4–7). Clear evidence of a more severe neurodevelopmental insult was not found, however; effect sizes observed in our study were similar to those seen in studies of patients with later-onset schizophrenia, with the ex-

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ception of a trend toward patients with childhood-onset schizophrenia having greater relative reduction in total cerebral volume (11).

Neurodevelopmental hypotheses of schizophrenia have emphasized the role of the temporal lobe and, particularly, medial temporal lobe pathology in the etiology of schizophrenic symptoms (1, 2). This notion is supported by postmortem (12, 13) and MRI (14–18) studies of adult patients with schizophrenia that found reduced hippocampal and amygdala volumes, although these findings have not been consistently replicated (19–22). In addition, MRI studies have demonstrated reduced temporal lobe (14, 23) and temporal lobe gray matter (24) volumes in patients with schizophrenia, again with notable exceptions (17, 21, 25, 26). Finally, reduced superior temporal gyrus volumes have also been observed in patients with schizophrenia (17, 27, 28), again with important exceptions (29, 30). Volume reduction in the left posterior superior temporal gyrus correlated significantly with the degree of thought disorder (27). In another study, volume reduction in the left superior temporal gyrus as a whole was related to auditory hallucinations (28).

In the present study, temporal lobe morphology for the 21 children and adolescents with treatment refractory childhood-onset schizophrenia described in our earlier study (11) was contrasted with that of 41 healthy children. Given the phenomenologic and neurobiological evidence for continuity between childhood-onset and later-onset schizophrenia (5, 7, 8, 11, 31), we expected that temporal lobe and medial temporal lobe structures would be reduced in our young patients with schizophrenia. On the basis of the preclinical model suggesting that earlier onset and/or more severe symptoms might be associated with a more severe neurodevelopmental lesion (10), we further hypothesized that relatively greater consistency or degree of volume reduction in temporal lobe structures would be found in this childhood-onset group. In addition, we anticipated that any reduction in volume of the superior temporal gyrus would be related to positive symptoms of psychosis.

METHOD

Subjects

Schizophrenic children and adolescents were recruited nationally for an ongoing study of childhood-onset schizophrenia involving a double-blind comparison of haloperidol and clozapine (5, 32). Inclusion criteria were DSM-III-R diagnosis of schizophrenia, onset of psychotic symptoms by age 12, premorbid full-scale IQ of at least 70, absence of active medical or neurological disease, and history of poor response to or inability to tolerate treatment with at least two different typical neuroleptics. Diagnosis was determined by using previous records, as well as clinical and structured interviews of the children and parents based on portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (33) and the Diagnostic Interview for Children and Adolescents-RC (DSM-III-R Version), Revised Version V-R (34).

The 21 subjects with schizophrenia included eight girls and 13 boys. They ranged in age from 10 to 18 years (mean=14.6, SD=2.1). All 21 had evidence of pubertal change (mean Tanner score=3.9, SD=1.1, range=2.0–5). Their mean age at the time of onset of psychotic symptoms was 10.2 (SD=1.5, range=7–12), and the group as a whole had undergone substantial treatment, both in terms of neuroleptic therapy (mean exposure=24.3 months, SD=17.5) and previous hospitalizations (mean=8.0 months, SD=10.6). These patients had no history of substance or alcohol abuse, and none had undergone ECT. Fourteen of the patients could be tested with the WISC-R (35); their mean full-scale IQ score was 82.1 (SD=16.8). Scores for three of these 14 subjects were estimated from scores on the vocabulary, block design, and digit span subtests of the WISC-R (36) because these patients were unable to complete the full test battery. MRI scans were obtained while subjects were receiving admission medications.

Forty-one normal children and adolescents, selected to be similar to the patients in age (mean=14.4, SD=1.7), sex (25 boys, 16 girls), and handedness, were recruited through advertisements. Medical, neurological, and psychiatric illnesses and learning disabilities were screened for by history from an interview with the parents, the Conners Preliminary Parent Report and the Achenbach Child Behavior Checklist (37) completed by parents, Conners Teacher Preliminary School Report and Conners Teacher Questionnaire (38, 39), physical and neurological examination of the child, and structured interview of the child and parent with the Diagnostic Interview for Children and Adolescents (DSM-III-R Version), Revised Version V-R. Any history of an axis I psychiatric disorder, learning disability, or mental retardation in a first-degree relative, according to parent report, was exclusionary.

Six of the patients with schizophrenia were left-handed, and 15 were right-handed; five of the normal children were left-handed, and 36 were right-handed. (Handedness was determined by using the 12 handedness items in the Revised Neurological Examination for Subtle Signs [40].) The mean height of the patients was 163.5 cm (SD=9.6), and their mean weight was 61.8 kg (SD=17.8). The mean height of the normal children was 164.8 cm (SD=13.2), and their mean weight was 55.4 kg (SD=10.9). The comparison subjects had above-average IQ (mean=118.7, SD=13.3), likely reflecting the strict inclusion criteria for the comparison subjects. (Full-scale IQ was estimated by using the vocabulary and block design subtests of the WISC-R [36].) The mean Tanner stage of these children was 3.6 (SD=1.4). Sociodemographic information was not available on normal children for comparison with that of the patients with schizophrenia.

Parents of all subjects provided written informed consent and subjects provided assent for participation in the study. This study was approved by the National Institute of Mental Health Institutional Review Board.

Assessments of Symptoms

Brief Psychiatric Rating Scale (BPRS) (41), Scale for the Assessment of Positive Symptoms (SAPS) (42), and Bunney-Hamburg psychosis subscale (43) scores were obtained for the patients with schizophrenia as described previously (32). Weekly scores obtained on each scale during a 4-week medication-free phase were averaged for use in this analysis. Interrater reliabilities (intraclass correlation coefficient [ICC]), based on ratings of 10 patients by two sets of child psychiatrists at two points in the study (one rater was consistent across both assessments), ranged between 0.64 and 0.90 for the BPRS, between 0.87 and 0.91 for the SAPS, and between 0.81 and 0.91 for the Bunney-Hamburg psychosis subscale.

MRI Image Acquisition

All subjects were scanned on a GE 1.5-T Signa magnetic resonance scanner. As described elsewhere (44), head position was stabilized with the use of foam padding. Head alignment was standardized by placing a vitamin E capsule in the meatus of each ear, taping one capsule to the left inferior orbital ridge, and then assuring that all three capsules were visible in the same axial reference plane. Subjects were scanned in the evening to promote their falling asleep in the scanner. Sedation was used with seven of the schizophrenic patients.

Data for temporal lobe volume measurements were derived from contiguous 2-mm-thick slices in the coronal plane, which were ob-

tained by using a three-dimensional spoiled gradient recalled echo in the steady state (time to echo=5 msec, repetition time=24 msec, flip angle=45°, acquisition matrix=192×256, number of excitations=1, and field of view=24 cm).

Image Analysis

Clinical interpretation. All scans were read by a clinical neuroradiologist, who found no abnormalities in scans of the normal children. One scan from the patient group was read as indicating enlargement of the left lateral ventricle, and another was read as having a focal area of increased signal in the left frontal white matter.

Total cerebral volume. Spatial orientation of the brain was standardized by using operator-selected midline anterior and posterior commissure points and the plane of the interhemispheric fissure. Brain matter was then separated from intracranial cavity, and right- and left-hemisphere volumes were quantified by using novel software based on a deformable surface model of the brain. This method employs an active surface template of a standard brain that is molded to fit the brain imaging data from specific subjects through successive iterations of an energy minimization function. Thus, the sometimes ambiguous MRI signal characteristics were supplemented by a priori knowledge of brain anatomy (45). Following this procedure, extracerebral material remaining in the resulting image was removed by manual editing of each axial slice (ICC=0.99). This method has been validated by using postmortem specimens, produces cerebral volumes that correlate highly (ICC=0.95) with volumes obtained by conventional manual measurement, and provides a measure of total cerebral volume that includes basal ganglia, thalamus, and ventricles and excludes cerebellum and brainstem.

Temporal lobe and superior temporal gyrus. Measurement of temporal lobe and medial temporal lobe structures was performed manually on sequential coronal slices by an experienced rater who was blind to subject identity and diagnosis (A.C.V.), using an image analysis program developed at the National Institutes of Health (46). Scans were assigned unique numbers and randomly intermixed with scans from other studies prior to measurement. Volumes were calculated by multiplying area by slice thickness.

The Sylvian fissure was used to distinguish temporal lobe from frontal and parietal cortexes. The temporal stem was delineated by a line connecting the most inferior point of the insular cisterns to the most lateral point of the basal cisterns above the hippocampus. The most posterior slice containing the splenium of the corpus callosum was designated as the posterior extent of the temporal lobes (47).

The superior temporal gyrus was identified by the gyral boundary in each of the coronal sections of the temporal lobes and traced throughout its extent. The most posterior slice containing fibers of the fornix was designated as the posterior boundary of this structure (27). In addition, superior temporal gyrus was divided into anterior and posterior segments; the anterior segment ended in the most posterior slice prior to the appearance of the mamillary bodies.

Amygdala/hippocampal complex. The slice immediately prior to the appearance of the mamillary bodies was designated as the posterior boundary of the amygdala (15, 18, 27). The first coronal slice containing the mamillary bodies marked the anterior boundary of the hippocampus, and the most posterior slice containing fibers of the fornix was its posterior boundary.

To assess reliability, 10 brains were remeasured by a second rater (J.N.G.). Ten brains were also remeasured by the first rater. For the temporal lobe, ICC=0.98; for the superior temporal gyrus, ICC=0.92; for the amygdala, ICC=0.86; and for the hippocampus, ICC=0.87.

Statistical Analysis

Group differences in demographic variables and total cerebral volume were assessed with chi-square analyses and t tests for independent samples. Temporal lobe and medial temporal lobe morphology was examined by using repeated measures analysis of variance (ANOVA) with diagnosis as a between-subjects factor and side as a within-subjects factor. Because volume of temporal lobe structures was highly correlated with total cerebral volume in both normal subjects and schizophrenic patients, these differences were reanalyzed with repeated measures analysis of covariance (ANCOVA) using total cerebral volume as a covariate. Significant interactions ($p<0.05$) were further examined with Bonferroni post hoc t tests. Regression slopes between total cerebral volume and temporal lobe volumes did not significantly differ between the two groups, indicating that the assumptions of ANOVA and ANCOVA were not violated.

Within the schizophrenic group, relationships between volumes of the superior temporal gyrus and its posterior segments and measures of positive symptoms obtained during the medication-free phase of the study were examined by using correlation analysis. Symptom ratings included in this analysis were BPRS conceptual disorganization score (item 4), BPRS hallucinatory behavior score (item 12), BPRS unusual thought content score (item 15), Bunney-Hamburg psychosis subscale score, sum of SAPS items 1 to 3 (auditory hallucinations) scores, and SAPS thought disorder subscale (items 26–34) score. Correlation analysis was also used to examine the relationships between temporal lobe variables and total number of months of neuroleptic exposure, lifetime chlorpromazine equivalents, admission neuroleptic dose in chlorpromazine equivalents, and duration of illness.

Chi-square analyses, t tests, ANOVA, and Pearson's correlation coefficients were computed by using SAS (48). ANCOVA was computed by using BMDP (49). All p values are two-tailed.

RESULTS

T tests revealed no significant differences between schizophrenic patients and normal subjects in age, height, weight, or Tanner stage. Similarly, chi-square analyses revealed no significant differences between the groups in sex or handedness. The groups did differ in mean full-scale IQ ($t=8.32$, $df=53$, $p<0.0001$) and mean total cerebral volume (1050 ml, SD=117, for schizophrenic patients compared with 1151 ml, SD=129, for normal subjects) ($t=3.11$, $df=60$, $p<0.01$); the total cerebral volume of schizophrenic patients was 8.8% smaller than that of normal subjects.

Analysis of Temporal Lobe and Medial Temporal Lobe Morphology

Mean unadjusted volumes of the temporal lobe, superior temporal gyrus, and amygdala/hippocampus complex of schizophrenic and normal children are displayed in table 1, along with the same measures adjusted for total cerebral volume. Table 2 shows the F and p values resulting from the ANOVA and ANCOVA.

Effects of laterality. Significant asymmetries (right greater than left) were found for the temporal lobe and the superior temporal gyrus, including its anterior and posterior segments. There were no significant diagnosis-by-laterality interactions for lateral temporal lobe structures, indicating that the diagnostic groups did not differ in the degree of lateralization across these structures. However, significant diagnosis-by-laterality interactions were demonstrated for medial temporal lobe structures. Examination of mean values and post hoc tests indicated that volumes of the amygdala were significantly asymmetric (right greater than left) in schizophrenic patients and not asymmetric in normal subjects. In contrast, volumes of the hippocampus were significantly asymmetric (right greater than left) in normal subjects but not asymmetric in schizophrenic patients.

TABLE 1. Temporal Lobe and Amygdala/Hippocampus Volumes of 21 Children and Adolescents With Childhood-Onset Schizophrenia and 41 Healthy Comparison Subjects

Brain Area	Unadjusted Volume (ml)								Mean Volume Adjusted for Total Cerebral Volume (ml)			
	Left				Right				Left		Right	
	Patients		Comparison Subjects		Patients		Comparison Subjects					
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Patients	Comparison Subjects	Patients	Comparison Subjects
Temporal lobe												
Total	83.1	11.0	87.0	12.5	88.2	14.4	89.7	12.3	87.8	84.6	92.9	87.4
Superior temporal gyrus												
Total	25.1	3.2	24.8	3.0	27.3	3.7	26.5	3.3	26.0	24.3	28.2	26.1
Anterior	10.8	1.8	10.8	1.8	11.7	2.6	11.3	2.2	11.1	10.6	12.0	11.1
Posterior	14.3	2.0	14.0	2.0	15.6	2.2	15.3	2.2	14.8	13.7	16.1	15.0
Amygdala/hippocampus complex												
Total	6.6	0.8	6.9	0.7	7.1	0.9	7.3	0.7	6.8	6.8	7.3	7.2
Amygdala	2.1	0.7	2.4	0.5	2.5	0.8	2.5	0.5	2.2	2.4	2.6	2.4
Hippocampus	4.6	0.6	4.5	0.6	4.5	0.5	4.8	0.5	4.7	4.4	4.6	4.7

Effects of diagnosis. Although ANOVA revealed no significant diagnostic differences, after adjustment for total cerebral volume with ANCOVA, several significant diagnostic differences emerged. Volumes of the superior temporal gyrus and its posterior segment were significantly and unexpectedly larger in schizophrenic patients than in normal subjects. Similarly, diagnostic differences for the temporal lobe approached significance (table 2); schizophrenic patients had larger volumes than normal subjects. Adding gender as a factor in the ANCOVA revealed evidence that the relatively larger superior temporal gyrus may be primarily driven by male schizophrenic patients and by right-sided volumes (diagnosis-by-gender-by-side interaction $F=3.73$, $p=0.06$, $df=1, 58$). Medial temporal lobe structures continued to exhibit no significant main effects of diagnosis following adjustment for total cerebral volume.

Given the unusual finding of larger volume of the superior temporal gyrus and its posterior segment and a trend toward larger temporal lobe volume in schizophrenic patients than in normal subjects after adjusting for total cerebral volume, we explored the possibility that these results could be due to differences in the shape of the temporal lobes between schizophrenic and normal children.

The possibility that the temporal lobes of schizophrenic patients were longer was tested by comparing the number of slices obtained from the point of the mamillary bodies to the most posterior boundary of the temporal lobes for the two groups. The groups did not significantly differ in the mean number of slices obtained in this region (16.8 for schizophrenic patients and 16.6 for normal children), indicating that the lengths of the temporal lobes were similar across groups.

The possibility that the temporal lobes differed in shape across diagnostic groups was tested by using repeated measures ANOVA with diagnosis as a between-subjects variable and slice area as a within-subjects variable. Slices between the mamillary bodies and the posterior boundary of the temporal lobes were examined. There was no effect of diagnosis or diagnosis-by-slice-number interaction, indicating that temporal lobe shape did not significantly differ between groups.

Because previous exposure to standard neuroleptics has been associated with increased volumes of basal ganglia structures (11, 50, 51), the relationship between exposure to standard neuroleptics and temporal lobe volumes was also examined. Total lifetime antipsychotic exposure (summed doses in chlorpromazine equivalents multiplied by length of trials) was negatively correlated with volumes of the left ($r=-0.44$, $N=20$, $p=0.05$) and right ($r=-0.55$, $N=20$, $p<0.05$) posterior segments of the superior temporal gyrus, indicating that treatment with standard neuroleptics cannot explain the relative increase in volume of temporal lobe structures in schizophrenic patients.

Relationship Between Symptoms and Temporal Lobe Morphology Within the Schizophrenic Group

Significant positive correlations were found between the BPRS conceptual disorganization score and volumes of the left superior temporal gyrus ($r=0.45$, $N=20$, $p<0.05$) and its posterior segment ($r=0.50$, $N=20$, $p<0.05$) and between the BPRS unusual thought content score and volumes of the left superior temporal gyrus($r=0.45$, $N=20$, $p<0.05$) and its posterior segment ($r=0.46$, $N=20$, $p<0.05$).

DISCUSSION

The absence of diagnostic differences across absolute values of the temporal lobe structures in patients with childhood-onset schizophrenia is consistent with much of the literature on temporal lobe morphology in later-onset schizophrenia (17, 21, 22, 25, 26, 30). Furthermore, the absence of diagnostic differences across both absolute and adjusted values for medial temporal lobe structures suggests that, in humans, earlier onset of

TABLE 2. Results of Repeated Measures Analysis of Variance (ANOVA) for Diagnosis, Laterality, and Diagnosis-by-Laterality Effects and Analysis of Covariance (ANCOVA) for Diagnosis in 21 Children and Adolescents With Childhood-Onset Schizophrenia and 41 Healthy Comparison Subjects

	Results of ANOVA (df=1, 60)							Results of ANCOVA With Total Cerebral Volume as Covariate (df=1, 59)		
	Diagnosis		Laterality		Diagnosis by Laterality					
Brain Area	F	p	F	p	F	p	Comment	F	p	Comment
Temporal lobe total	0.74	n.s.	9.43	<0.01	0.87	n.s.	Right > left	3.68	0.06	Patients > comparison subjects (trend)
Superior temporal gyrus										
Total	0.52	n.s.	20.81	<0.001	0.22	n.s.	Right > left	8.33	<0.01	Patients > comparison subjects
Anterior	0.22	n.s.	4.06	<0.05	0.32	n.s.	Right > left	3.16	n.s.	
Posterior	0.39	n.s.	54.82	<0.001	0.00	n.s.	Right > left	4.81	<0.05	Patients > comparison subjects
Amygdala/hippocampal complex										
Total	1.73	n.s.	43.41	<0.001	0.27	n.s.	Right > left	0.15	n.s.	
Amygdala	1.37	n.s.	7.20	<0.01	5.49	<0.05	Patients: right > left; comparison subjects: right = left	0.03	n.s.	
Hippocampus	0.58	n.s.	4.72	<0.05	6.32	<0.05	Patients: right = left; comparison subjects: right > left	0.48	n.s.	

schizophrenia is not the result of a more severe medial temporal lobe lesion. Finally, the finding of robust right-greater-than-left-laterality effects across temporal lobe structures and diagnostic groups also replicates findings in normal adults and children and in schizophrenic adults (17, 24, 26, 52, 53).

The emergence, after adjusting for total cerebral volume, of relatively larger volumes of the superior temporal gyrus and its posterior segment is unique and, therefore, must be viewed with caution. The importance of adjusting for brain size differences when comparing diagnostic groups was recently underscored by Schultz et al. (54), who noted that differences between dyslexic and normal children in planum temporale morphology disappeared following correction for brain size. Comparable loss of diagnostic differences in temporal lobe volumes with adjustment for brain size has been observed in later-onset schizophrenia (25).

The fact that other brain morphology in patients with childhood-onset disorder resembles the pattern of abnormalities typically seen in later-onset schizophrenia (11) suggests that these unusual temporal lobe findings might represent a relative sparing of lateral temporal lobe structures that is unique to childhood-onset schizophrenia. Since the temporal lobe and superior temporal gyrus do not change in size during normal development (52), it is unlikely that the relative enlargement of these structures in childhood-onset schizophrenia is the result of a failure of normal pruning. Rather, a sparing from an as-yet-unknown process that decreases the size of other brain areas in these patients appears to be occurring.

The suggestion that relative sparing of the superior temporal gyrus may be specific to male schizophrenic patients, if replicated, is consistent with data from adult studies indicating that males and females may develop schizophrenia via different neurodevelopmental routes (55–57). The higher rates of prematurity, early speech difficulties, and features of pervasive developmental disorder, as well as the insidious onset of illness among the boys in the present group of patients with childhood-onset schizophrenia are also consistent with a gender-specific vulnerability (8).

The absence in schizophrenic patients of the normal right-greater-than-left asymmetry in the hippocampus is consistent with observations of loss of normal asymmetry of cerebral structures in later-onset schizophrenia (29, 47, 58). On the other hand, the absence of right-greater-than-left asymmetry for the amygdala in normal subjects is probably an artifact of the size of the study group because our larger series of normal children and adolescents did demonstrate the expected right-greater-than-left asymmetry for this structure (52).

The significant positive correlations between the volume of not only the left superior temporal gyrus but also its posterior segment and measures of thought disorder and psychosis stand in direct contrast to previous reports of a negative correlation between these variables in later-onset schizophrenia (27, 28). This finding is consistent, however, with the association between greater deviation from normal superior temporal gyrus morphology and more severe positive symptoms.

Of course, replication of these findings with larger numbers of subjects, permitting examination of gender effects, is needed. In addition, the inclusion criterion of previous nonresponse to typical neuroleptic medication may have functioned to select a subset of patients with childhood-onset schizophrenia who had greater brain abnormalities (59). However, phenomenologic similarities between this group of subjects and other study

groups of patients with childhood-onset schizophrenia (4, 6, 7) suggest that these findings are relevant to childhood-onset schizophrenia in general.

Ongoing analyses of brain morphology in this rare group of children and adolescents with childhood-onset schizophrenia, including regional gray/white volumes and longitudinal rescan, may provide further clues as to the brain developmental events triggering schizophrenia at the unusually early age at onset in these children.

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